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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/846,033

04/30/2001

Edward Rebar

019496-005820US

4301

20350

7590

11/12/2003

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EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 11/12/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

RUBEN

Office Action Summary

Application No.

09/846,033

Applicant(s)

REBAR ET AL.

Examiner

Jegatheesan Seharaseyon

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26,67-71,75-79 and 95 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26,67-71,75-79 and 95 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 17 & 18. 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's election without traverse of Group III, claims 26, 67-71, 75-79 and 95, drawn to a method of modulating VEGF genes comprising administering a zinc finger protein in Paper No.: 20 is acknowledged. Applicants have also cancelled claims 1-25, 27-66, 72-74 and 80-94. Applicants have further elected VOP32E protein and activation of VEGF expression and stimulation of angiogenesis. The restriction requirement is still deemed proper and therefore made FINAL. Therefore, claims 26, 67-71, 75-79 and 95 are examined on the merits.

Priority

2. Applicant is required to update the current status of the priority Applications.

Information Disclosure Statement

3. Applicant has provided information disclosure papers on 12/18/01 (Paper No: 10), 10/07/02 (Paper No: 17) and 1/21/03 (Paper No: 18). However, the IDS from 12/18/01 is missing from the file and thus was not considered for this Office Action.

Claim Objections

4. Claims 68, 69, 70, 75, 78 and 79 are objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification and the claims. See 37 CFR § 1.821(d). Applicant is required to recite the specific SEQ ID Nos of the zinc finger proteins in the claims instead of referring to the tables.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1647

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26, 67-71, 75-79 and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claim 26 is rejected as vague and indefinite because it recites a desired outcome and not a method step. In addition, it does not further limit the recitation of claim 67.

The expression of a plurality of splice variants is inherent to the expression VEGF gene.

5b. Claims 67 and 71 are rejected as broad for reciting the term "modulating" because the term "modulating" implies both inhibiting and stimulating. It is unclear how the zinc finger binding at a target site in the VEGF gene can both inhibit and stimulate angiogenesis. Claims 26, 68, 69 and 70 are rejected insofar as they are dependent on the rejected claim 67.

5c. Claims 26, 67, 71, 76 and 95 are rejected as vague and indefinite for reciting the term "VEGF" because the full meaning of an acronym should be spelled out at its first use in any claim. Claims 68, 69 and 70 are rejected insofar as they are dependent on the rejected claim 67.

5d. Claim 71 is rejected as being vague and indefinite because it is unclear if the plurality of VEGF genes referred to be in the same organism or else from different organisms.

5e. Claim 76 is rejected as being vague and indefinite because it does not further limit the recitation of claim 75. It is not clear whether there is an animal genome which does not contain the VEGF gene. The presence of VEGF gene in the genome is inherent to

Art Unit: 1647

the animals. Claims 77, 78 and 79 are rejected insofar as they are dependent on the rejected claim 76.

5f. Claim 76 is rejected as being vague and indefinite because it is unclear if the introduction of the zinc finger protein needs to be at the wound or whether systemic administration is envisioned.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6a. Claims 26, 67-71 and 75-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al. (1997) in view of Cox, III et al. (U.S. Patent No: 6,534,261).

The instant invention is directed to modulating angiogenesis by introducing zinc finger protein into an animal to a target site on VEGF gene. It is also directed to treating ischemia and wound healing.

Ferrara et al. describe the role of vascular endothelial growth factor (VEGF) in the regulation of angiogenesis. The reference also teaches that VEGF has pivotal role in the normal and abnormal angiogenesis (page 4, introduction). Furthermore, it also teaches the various splice variants of VEGF genes (pages 5-6). Ferrara et al. also discuss the regulation of VEGF gene expression by transcription regulatory factors including hypoxia-inducible factor 1 (page 7). It also discusses the therapeutic applications of VEGF-induced angiogenesis, specifically in the treatment of ischemia (paragraph bridging pages 17-18). Ferrara also discloses the modulation of VEGF expression in order to treat several pathological conditions (pages 14-19). However, Ferrara et al. does not teach the modulation of VEGF gene expression by the introduction of zinc finger protein to target of VEGF gene.

Cox et al. discloses regulation of endogenous gene expression in cells using zinc finger proteins. They disclose the discovery zinc finger proteins (ZFP) that bind to specific DNA targets (column 2, lines 43-44). Cox et al. discloses that the recognition of the structural features unique to the Cys₂–His₂ (C₂H₂) class of nucleic acid-binding, zinc finger proteins. The C₂H₂ zinc finger domain is approximately 30 amino acids in length (column 2, lines 48-51). The structure suggests that each finger interacts independently with DNA over 3 base-pair intervals, with side chains at positions –1, 2, 3 and 6 on each recognition helix making contacts with respective DNA triplet sub-site (column 2, line 66

Art Unit: 1647

to column 3, line 2). It also teaches the modulation of endogenous cellular genes (column 51, lines 28-33). In examples VI and VII the authors teach the repression and activation VEGF gene (column 51 and 52). It also contemplates *in vivo* applications (column 27).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to regulate VEGF gene in order to regulate angiogenesis as described by Ferrara et al. by introducing a zinc finger protein (transcription regulatory factor) into an animal to target a site within VEGF gene as taught by Cox III et al., with the expectation of modulating the expression of VEGF gene. One of ordinary skill in the art would have been motivated to modulate angiogenesis by regulating the expression of VEGF gene by introducing zinc finger protein to target a site on VEGF gene to regulate the VEGF gene expression as taught by Cox III et al. In addition, regulating angiogenesis will enable one to treat diseases such as ischemia as described in Ferrara et al. Therefore, the instant claims are *prima facie* obvious over Ferrara et al. (1997) in view of Cox, III et al. (U.S. Patent No: 6,534,261).

6b. Claim 95 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al. (1997) and Baird et al. (U.S. Patent No: 6,479, 654) in view of Cox, III et al. (U.S. Patent No: 6,534,261).

The instant invention is directed to modulating angiogenesis by introducing zinc finger protein into an animal to a target site on VEGF gene. It is also directed to treating ischemia and wound healing.

The teachings of Ferrara et al. and Cox III et al. have been described above in paragraph 4a. However, the references do not the role VEGF in wound healing. Baird et al. teach that the upregulation VEGF after hypoxia is essential for wound healing (column 3, lines 1-5). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to up regulate the VEGF gene in order to regulate angiogenesis as described by Ferrara et al. by introducing a zinc finger protein into an animal to target a site within VEGF gene as taught by Cox III et al. with the expectation of modulating the expression of VEGF gene. One of ordinary skill in the art would have been motivated to modulate angiogenesis by regulating the expression of VEGF gene by introducing zinc finger protein to target a site on VEGF gene to regulate the VEGF gene expression as taught by Cox III et al. In addition, regulating angiogenesis will enable one to treat conditions such as wound healing as described in Baird et al. Therefore, the instant claims are *prima facie* obvious over Ferrara et al. (1997) and Baird et al. (U.S. Patent No: 6,479,654) in view of of Cox, III et al. (U.S. Patent No: 6,534,261).

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Rebar et al. Induction of angiogenesis in a mouse model using engineered transcription factors (2002), Nature Medicine, Vol.18, NO. 12, pp; 1427-1432.

This is applicants own work published after the filing of the application.

8. No claims are allowable over prior art.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS



LORRAINE SPECTOR
PRIMARY EXAMINER